NATIONAL INSTITUTES OF HEALTH

FISCAL YEAR 2005

PLAN FOR HIV-RELATED RESEARCH

X: INTERNATIONAL RESEARCH

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

OFFICE OF AIDS RESEARCH

AREA OF EMPHASIS:

International Research

SCIENTIFIC ISSUES

Now entering its third decade, the AIDS epidemic continues its relentless spread across the globe. The devastating effect of AIDS is broad, impacting on households, education, enterprises and workplaces, the health sector, and the macroeconomics of countries. AIDS is inextricably linked with other crises, such as war and famine. As the Joint United Nations Programme on HIV/AIDS (UNAIDS) notes in its December 2002 Report *AIDS Epidemic Update,* AIDS is fueling famine in Southern Africa. According to UNAIDS worldwide estimates, at the end of 2002:

- 42 million people worldwide were living with HIV/AIDS;
- 3.2 million were children under the age of 15 years;
- 19.2 million (50 percent) of infected adults were women;
- Five million new HIV infections (adults and children) had occurred during 2002; and
- In 2002 alone, HIV/AIDS had killed 3.1 million people.

Referring to the most affected region in the world, sub-Saharan Africa, UNAIDS in its Report declared that "The worst of the epidemic clearly has not yet passed." There were 29.4 million people living with HIV/AIDS in sub-Saharan Africa at the end of 2002; 3.5 million new infections occurred that year. What is happening in sub-Saharan Africa illustrates the devastation

HIV infection can bring to a people and foreshadows what lies ahead for other regions, if the world does not mount a comprehensive campaign to address HIV. Epidemics have long been established in Latin America and the Caribbean. The Caribbean is the most affected region in the world after sub-Saharan Africa, with an overall prevalence rate of 2.4 percent among adults. Haiti has the highest adult prevalence rate (over 6 percent), followed by the Bahamas, with an adult prevalence rate of 3.5 percent. Meanwhile, the epidemic in Central America is worsening, particularly among the socially marginalized sections of the population.

In other regions of the world, HIV/AIDS epidemics are rapidly escalating. In Asia and the Pacific region, 7.2 million persons are now infected, a 10 percent increase over the previous year. While this region currently accounts for 20 percent of annual new infections, the region is predicted to account for 40 percent of all HIV infections that will occur between 2002 and 2010, if the disease is allowed to continue unabated. The Eastern European and Central Asian region has the fastest-growing HIV/AIDS epidemic in the world, with 1.2 million people living with HIV/AIDS. For example, in the first 6 months of 2002, there were almost as many new infections reported in Uzbekistan as had been recorded in the previous decade. In the Russian Federation, which is experiencing an especially steep rise in HIV infection, transmission is attributed to injecting drug use in 90 percent of reported cases.

In spite of these discouraging figures and projections, the UNAIDS Report is optimistic that the pandemic can be brought under control. Successes throughout the world serve as models for others. However, to stem the tide, it is critical to continue the fight against HIV/AIDS on all fronts: to develop and implement approaches to prevention, treatment, and care.

Research is an essential component of a comprehensive approach to address the global pandemic. Since the early days of the epidemic, the NIH has supported research efforts in countries impacted by HIV and AIDS. Beginning in 1984 with a research project in Haiti and the establishment of Projet SIDA in 1985 in what was then Zaire, the NIH has maintained a strong international research portfolio. Development of a research infrastructure, including training of scientists and health care providers, is an essential adjunct to these research programs. The NIH has expanded its research effort to encompass more than 50 countries around the world, and collaborations between scientists in the United States and in developing countries have provided much valuable information. Results of this research benefit not only the people in countries where the research is conducted, but people affected by HIV/AIDS worldwide.

Decisions about sites for future research are guided by scientific opportunities that arise as a result of scientific advances, as well as the continuing evolution of the pandemic. Thus, the research portfolio continues to grow and evolve. In 2000, the Office of AIDS Research established a new initiative and plan for global research on HIV/AIDS. The Plan was included as part of the *FY 2002 NIH Plan for HIV-Related Research* and has now become part of the annual AIDS planning process. In the planning and implementation of the international AIDS research portfolio, the NIH collaborates with in-country scientists, UNAIDS, the World Health Organization (WHO), host country governments, foundations, and nongovernmental organizations (NGOs).

There is an urgent need in resource-poor countries for culturally appropriate and effective interventions to prevent transmission of HIV and to treat HIV and associated complications in both adults and children, integrating prevention and care to optimize access to services. An integral component of research to develop these interventions must include research to examine biological, behavioral, and social factors affecting transmission and clinical management of infected patients. Although the treatment research focus is on the development of therapeutic strategies for primary HIV infection and related conditions, it will still be critical to conduct research on palliative care appropriate for use in these settings. As part of this overall effort, there is a pressing need for better evaluation methods that can be used for both prevention and treatment programs as they are implemented.

To combat the pandemic, it is essential to implement the results of research that have an impact on affected populations. Information gained through research must be translated into activities that will enhance patient management, improve prevention programs, and inform policy decisions in resource-poor settings around the world. Accomplishing this goal requires that research results be made available to policymakers in foreign governments, as well as to NGOs and international organizations that develop programs to deliver health care, prevention, and other services. To facilitate this process, the conduct of operational research is of critical importance to better understand how to develop and implement programs in the relevant country context.

Research also is needed to better understand how to combat stigma at all levels, since stigma is associated with AIDS in virtually every setting. Government leaders have been reluctant to acknowledge the presence of an AIDS epidemic; communities have shunned entire social groupings because of their association with AIDS; families have rejected HIV-infected

family members or hidden their illness; and individuals have been reluctant to disclose their status for fear of discrimination in all aspects of their lives. Both HIV-infected and HIV-uninfected at-risk individuals suffer from stigma, as do those who provide care for these people. Stigma prevents infected individuals from being tested for HIV and from seeking or utilizing prevention and care services even where they are available, which impacts negatively on their own health and the health of their sexual partners and family members. Stigma also prevents individuals from using prevention strategies even when they are simple, affordable, and practical. Thus stigma fuels the epidemic by inviting the further spread of HIV infection.

There is great diversity among international settings with respect to prevention and treatment research needs, and an overriding principle guiding the conduct of NIH-supported international AIDS research is that the research effort must be relevant to the cultural, social, and economic context of the country where the research is conducted. Two steps to accomplish this are involving the local community throughout the development of the research effort and ensuring a leadership role for in-country scientists. Related to this principle is the need to be mindful that countries differ greatly as to the economic and other infrastructure resources available to implement the results of research. Thus, in-country and U.S. investigators must work together to assess the local needs, design research studies to address them, and then conduct the research through collaboration.

INFRASTRUCTURE FOR RESEARCH ON NEW INTERVENTIONS

PRIORITY FOR FUTURE RESEARCH:

- **Develop in-country research and training infrastructure for the conduct of effective prevention and treatment interventions research, integrating new activities into existing health care and prevention services where possible.**

Various sections of the Plan describe NIH research efforts to develop HIV vaccines; chemical and physical barrier methods, such as microbicides, to prevent sexual transmission; behavioral strategies targeted to the individual, family, and community to alter risk behaviors associated with sexual activity and drug and alcohol use; drug and nondrug strategies to prevent mother-to-child transmission (MTCT); therapeutics for HIV-related co-infections and other conditions; and approaches to using antiretroviral therapy (ART) in resource-poor settings. But before prevention and treatment interventions can be implemented in different geographic settings, their safety and efficacy must be demonstrated in such settings through clinical trials and other intervention research. In resource-poor countries, adequate infrastructure may not exist to conduct such trials and must be developed.

Several principles guide the development of infrastructure. One is that many of the clinical and infrastructure needs for clinical trials are developed *through* the conduct of research in these settings, reinforcing the need to support ongoing clinical and population-based research as preparation for eventual clinical trials. In addition, infrastructure development is enhanced when the research effort is integrated with ongoing health care and prevention services and when prevention and care services themselves are integrated, enabling prevention messages to be delivered in the care setting.

Specific infrastructure needs are many. In order to move quickly with clinical trials of promising products and strategies, research sites must be strengthened through establishment of stable, targeted cohorts; development of recruitment and retention strategies; and enhancement of laboratory, clinical, and data management capabilities. To ensure the leadership role of in-country researchers, it is critical that in-country personnel have the major responsibility for the conduct of the research. Thus, it is critical to increase the number of scientists, clinicians, and health care workers of all levels and disciplines who are trained in basic, clinical, and behavioral research; data management; program management and administration; and ethical considerations. To maximize the development of human resource-related, in-country research infrastructure, it is essential to develop strategies to retain researchers in-country and enhance the careers of trained personnel. Alongside the need to train and retain researchers is the need to develop strong and effective research collaborations involving both U.S. and foreign colleagues. Finally, it is essential to transfer appropriate clinical and laboratory technologies to in-country settings. Critical to the effort to strengthen infrastructure is the need to devise innovative funding mechanisms and approaches, such as the evolving policy on provision of indirect costs to foreign institutions.

HIV-RELATED ILLNESS IN DIVERSE GEOGRAPHIC SETTINGS

PRIORITY FOR FUTURE RESEARCH:

- **Define the spectrum of HIV-related illnesses in diverse geographic settings and develop effective prevention and treatment interventions to limit their impact, with special emphasis on tuberculosis.**

Since the beginning of the epidemic in the United States, research has been conducted to characterize a variety of opportunistic infections (OIs). Methods for diagnosis, prevention, and treatment of OIs have been developed. Recently, the extensive use of effective ART has resulted in a dramatic decrease in many of these conditions. In the developing world, such conditions remain the cause of morbidity and mortality associated with HIV infection. Although much research has been conducted in these

countries concerning the natural history of HIV disease, much remains to be elucidated about the extent of endemic co-infections, cancers, neurologic manifestations, and other conditions associated with HIV infection in these settings. It is necessary to develop and assess vaccines and drugs to prevent and treat them, particularly since antiretroviral drugs (ARVs) are only beginning to be used in these settings and may not be widely used for some time. The needs of both adults and children must be addressed in these efforts. As a foundation for the development of such interventions, it is essential to characterize the nature, prevalence, risk factors, and disease course of endemic co-infections, as well as other HIV-related conditions found in diverse geographic settings. An integral component is the development of diagnostic methods to detect these illnesses.

The relationship between HIV infection and other sexually transmitted diseases (STDs) has long been understood. However, important new information about the global extent and nature of concomitant infection with hepatitis C virus (HCV) is just beginning to emerge, and research is needed to further characterize the extent and nature of HIV/HCV co-infection. The HIV-related global epidemic of tuberculosis (TB) is well documented, with approximately a third of the world's population of HIV-infected individuals co-infected with *Mycobacterium tuberculosis*. Escalating TB rates are largely due to HIV in areas such as sub-Saharan Africa because HIV is a known risk factor for reactivation of latent TB, and HIV-infected persons who become infected with *M. tuberculosis* more rapidly progress to active TB. TB is now the leading cause of death among HIV-infected individuals worldwide. Thus, research to develop approaches to prophylaxis and treatment of TB remains a priority.

Further, little is known about other infections and conditions. It might be expected that the occurrence of conditions varies greatly depending on geography. For example, fungal infections might prevail in one setting and bacterial infections in another. The background presence of specific cancers might affect the pattern of HIV-related cancers. Diseases not found in industrialized nations may be important in more resource-diverse regions. For example, it has been demonstrated that a fungal infection due to *P. marnefii* is a significant co-infection in Thailand, where scientists have developed an effective treatment for it. In addition, as therapies and prophylaxis strategies are developed for co-infections, it will be critical to examine the impact of new interventions on diseases not previously thought to be related to HIV but that are endemic to the region, such as malaria.

At the same time, in the United States, extended survival has been associated with the development of new conditions, some of which result from the treatment itself (e.g., metabolic disorders). As the use of ART increases in the developing world, it will be necessary to characterize conditions that emerge in these settings, since factors such as diet, the presence of endemic diseases, and the use of drugs to treat them may affect the nature and occurrence of such conditions. In addition to comorbid diseases, it also is important to address co-occurring conditions that affect HIV transmission, disease progression, treatment, and prevention, including substance abuse, mental illness, and violence.

USE OF ANTIRETROVIRAL THERAPY

PRIORITY FOR FUTURE RESEARCH:

- **Study the appropriate introduction and long-term use of ART in resource-diverse settings.**

The use of ART has extended the length and improved the quality of life for many HIV-infected people in industrialized countries. Unfortunately, these therapies have not been widely utilized in resource-poor nations due to factors such as cost and the need for an adequate health care infrastructure to administer and monitor complex therapeutic regimens of toxic agents. However, momentum has grown to provide options for the use of ART in these regions. It is therefore critical to move rapidly to investigate the safety and efficacy for both adults and children of various ART regimens in diverse resource-poor settings. For example, differences in diet, nutritional status, or the use of medications for endemic diseases may alter the toxicity or the efficacy of ARVs as compared with industrialized areas. As the world progresses to more widely implement ART, more information is urgently needed in order to ensure optimal treatment approaches. Practice in industrialized countries may not be directly applicable due to many factors such as existing health care infrastructure, social structure, and the presence of other endemic diseases, as well as factors related to the patients themselves and their families. Thus, questions about when to initiate treatment, which drugs to use, and how to monitor patients and adjust treatment regimens must be answered for individual developing country settings. It also will be critical to ensure that regimens selected for study are appropriate for long-term sustainability in the context of specific geographic settings. Related research includes studies of adherence to prevent the development of drug resistance and studies of high-risk behavior change that may occur when ART becomes available. Alongside research on implementation of ART, methodologies must be developed to enable scale-up of programs to provide ART.

In order to move rapidly in this field, the laboratory and human resource infrastructure already established in the developing world needs to be further developed specifically for treatment research, including the training of in-country scientists, clinicians, and other health care workers. In addition, appropriate approaches must be determined for use in these settings to monitor patients for treatment efficacy and toxicity, both in order to conduct clinical trials and to establish treatment guidelines for developing countries. Questions must be addressed about the implementation of current technologies for viral load and CD4+ cell counts and the development of lower-cost methods and alternatives for these tests. The need to move rapidly will require the use of creative and flexible funding mechanisms. Finally, it is critical that dialogue is initiated early with the pharmaceutical industry concerning the provision of drugs for the research effort and for treatment regimens once they have been demonstrated safe and efficacious.

PREVENTION OF TRANSMISSION

PRIORITY FOR FUTURE RESEARCH:

- **Support studies to develop prevention interventions appropriate to particular settings, with a particular focus on addressing prevention of HIV transmission from mother to child and drug and alcohol use and their associated risks in transmitting and acquiring HIV infection.**

An effective vaccine remains the ultimate weapon to stem the pandemic, but until a vaccine is developed, other prevention interventions must be developed and implemented. Thus, the NIH is pursuing international research in all these areas simultaneously—from basic research on genetic diversity to assist in vaccine development to the development of structural interventions. From a global perspective, the major modes of acquiring HIV infection are unprotected heterosexual intercourse and injecting drug use, with the vast majority of infections occurring through sexual transmission. Appropriate and acceptable biomedical and behavioral interventions to curb this transmission in very diverse settings are urgently needed, interventions that must address specific populations at risk, such as women and adolescents. Behavioral and social interventions are needed at all levels: individual, family, social network, community, and society. These interventions must address seropositive individuals as well as those who are seronegative. Women are particularly vulnerable, comprising 47.6 percent of adults worldwide who became infected during 2002. It is critical to develop microbicides and other prevention methods that can be controlled by women. It also is important to address social factors that contribute to vulnerability to HIV transmission and that serve as possible points of intervention. These include stigma and discrimination, war, migration, poverty, gender inequality, and famine. Research also is needed to devise strategies to decrease transmission in medical settings.

Two prevention intervention needs merit special attention: prevention of MTCT and transmission related to drug and alcohol use. Since 1994, industrialized nations have experienced a dramatic decrease in MTCT through the use of a complex regimen of ARVs, coupled with access to voluntary counseling and testing and avoidance of breastfeeding. However, preventing MTCT is a significant challenge in resource-poor settings of the world, where these regimens are too expensive and complex to implement; operative delivery may not be safe and could threaten the health of the mother; and HIV-infected women continue to breastfeed due to stigma and the lack of safe, sustainable, affordable, and acceptable alternatives to breastfeeding. While clinical trials have demonstrated that a variety of short, simple, effective, and inexpensive ARV regimens also can reduce MTCT by up to 50 percent, the results have been slow to be implemented, and postnatal transmission through breastfeeding remains a significant problem. The U.N. Declaration of Commitment on AIDS includes as a goal to reduce the proportion of infants infected with HIV by 20 percent by 2005 and 50 percent by 2010. In order to reach this goal, new interventions will need to be developed to further reduce MTCT, particularly through breastfeeding, and operations research will need to be conducted to facilitate implementation of effective regimens.

UNAIDS reports that injecting drug use is a growing factor in the AIDS epidemic, estimating that about 10 percent of HIV infections globally result from this practice. Injecting drug use is fueling epidemics in Central and Eastern Europe and countries of South and Southeast Asia, where in some countries, more than half of HIV infections are attributed to injecting drug use. In the Russian Federation, which is experiencing an exceptionally steep rise in HIV infection, transmission is attributed to injecting drug use in 90 percent of reported cases As a social phenomenon, injecting drug use itself is reported to be growing in all regions of the world, including Africa. Thus the potential exists for drug-related epidemics to arise in new places and for escalation of established epidemics. Injecting drug users who share needles and other contaminated equipment are at high risk of acquiring or transmitting HIV as well as other blood-borne pathogens, such as HCV. However, the use of noninjecting drugs, including alcohol, also is associated with increased risk, particularly through associated sexual behavior. Of great concern is the use of alcohol and other drugs among young people. Alcohol is related to dis-inhibition, and as the most widely used drug in the world, may be associated with the spread of HIV in a variety of social contexts. For example, alcohol can be responsible for an increase in risky sexual behaviors and with the loss of inhibitions that normally guard against the use of injecting drugs. In many parts of the

world, drug use and sexual transmission of disease are inextricably linked, and drug users are more likely to be involved in the sex industry, greatly enhancing their risk of infection and the chances of HIV spreading even wider in the community. Injecting drug users are particularly vulnerable to HIV and AIDS because they are often poor and marginalized. To prevent transmission related to drug and alcohol use, culturally relevant interventions are needed at all levels: individual, social network, community, and society. Interventions are needed to (1) prevent the initiation of drug use and alcohol dependence; (2) prevent the transition to riskier drug use (e.g., alcohol to other drugs; noninjecting to injecting drug use); (3) prevent transmission through high-risk sexual behavior related to drug or alcohol use; (4) treat drug addiction; and (5) address the transmission of other diseases, such as hepatitis C, through the same routes. To ensure that newly developed interventions are culturally appropriate, it is critical to conduct research to better understand the social context of drug and alcohol use and to involve the community at all levels of the research.

BARRIERS TO INTERNATIONAL RESEARCH

PRIORITY FOR FUTURE RESEARCH:

- **Address challenges and barriers that impede the conduct of international research.**

Many challenges exist to the conduct of research in resource-poor settings. The development of research infrastructure through training of researchers, strengthening of laboratory and clinical capacity, and development of research collaborations will help to address many of these challenges. However, other barriers remain that will need to be addressed. These include barriers operating at the institutional level, as well as barriers for individuals that come about as a result of existing social and cultural norms.

Ethical considerations must be paramount in the development of international collaborations and NIH support of research activities in other countries. It is universally accepted that researchers should adhere to and address standard ethical principles in the design and conduct of research. Essential to the protection of human subjects participating in research, these principles are outlined in several documents and include respect for persons, beneficence, and justice. However, the vastly different economic and cultural contexts in which research is conducted in international settings create many challenges for researchers and funding agencies in the application of these principles. For example, obtaining voluntary informed consent from each study participant may be complicated in some settings by social customs requiring the involvement of others in the community in this process, such as family members or community leaders;

lengthy and complex informed consent forms used in the United States may be problematic to use in these settings. Differences in law, regulation, and public policy, as well as organizational structures, mean that careful consideration must be given to how ethical standards of both the United States and the country where research is conducted can be met. Dialogue is needed to reach common understanding of the application of U.S. and foreign ethical standards and should include U.S. and foreign investigators, staff of the Office for Human Research Protections, NIH program managers, and nongovernment ethicists.

Similarly, compliance with regulatory requirements in resource-poor settings is a challenge. The randomized clinical trial "gold standard" is difficult to implement and may not even be appropriate for some types of research. In addition, just as there is great difference between clinical hospital sites in the United States and developing countries, there also is a great difference between developing country hospitals and field sites in their capacity to implement regulatory requirements. Further, issues related to treatment trials may not be relevant to other research efforts. For example, training in Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) is essential for the conduct of clinical trials but may not be necessary for other studies. In this regard, it is critical to address early in the research planning process whether or not the research is intended to support product approval by the U.S. Food and Drug Administration (FDA). Dialogue similar to that for ethics is needed to develop common understanding of the application of regulatory requirements and should include U.S. and foreign investigators, staff of the FDA, NIH program managers, and industry representatives as appropriate.

Several issues related to ART and international research are currently topics for ongoing policy development. These include the use of research funds to acquire drugs (or other products) for clinical trials; the provision of ART to study participants at the end of treatment trials; and referral to treatment programs for individuals shown to be seropositive during screening for entry into clinical trials and other studies and for those who seroconvert during the course of a vaccine or other prevention trial. Clearly, these issues have substantial ethical, financial, and organizational ramifications for NIH-supported research.

Additional institutional challenges include the need to link research programs with prevention, treatment, and care programs, integrating prevention and care where possible; enhancing the ability of study sections and review groups to address proposals for international research; and developing the expertise of program staff to manage international research

portfolios. In addressing all these institutional issues, coordination among funding agencies—within the United States and around the world—will be critical. The establishment of a database that tracks ongoing efforts funded through a variety of mechanisms would be of great assistance in such coordination. In addition, a single, comprehensive source of information relevant to the conduct of research, such as application procedures, ethical and regulatory requirements, and other policy issues would be of great assistance to foreign investigators and their U.S. collaborators.

A number of interrelated issues act as barriers to international research by impacting on access of individuals to clinical studies. These social and cultural issues include gender inequities, poor health-seeking behaviors, and stigma. Since the earliest days of the epidemic, stigma has been associated with AIDS. Much of this stigma is related to the modes of transmission, and its impact is evident at government, societal, family, and individual levels, as well as in the health care setting. Stigma prevents individuals from participating in clinical studies, due to fear that a positive serostatus would become known to family and community members, fear that a positive serostatus might be presumed simply because of participation, or fear of being thought to be a member of an at-risk group. Stigma is compounded by gender inequities, and women have less access than men to clinical studies—and therefore to the benefits of participation. Both men and women may have poor health-seeking behaviors because of other economic or familial pressures, and many times it is those who need it most that do not access services. Thus, strategies are needed to combat stigma, address gender inequities, and improve health-seeking behaviors, particularly of infected and at-risk populations in resource-poor settings.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE - A:

Build sustainable research capacity in international settings that will: (1) provide an environment that promotes the development of equal partnerships between U.S. and foreign investigators; (2) facilitate the conduct of basic and clinical biomedical, sociocultural, and behavioral research and long-term cohort studies; (3) serve as loci for studies of prevention and treatment interventions, including studies of the safety, efficacy, and effectiveness of these interventions; (4) train investigators from country and regional programs; and (5) integrate with programs that provide services, thereby offering opportunities for the study of models of effective and cost-effective delivery of care such as those that integrate prevention and care.

STRATEGIES:

Site Development

- Assess existing sites and, as needed, further develop existing or establish new international research sites as rapidly as possible, addressing geographic regions and specific populations where HIV is and/or will be a major cause of morbidity and mortality.
- Enhance capacity for the conduct of basic and applied research, clinical trials, health services research, and studies of the clinical aspects of HIV and related conditions, with emphasis on GCP of the intensity and rigor needed for large-scale trials through:
  - conducting ongoing incidence assessments in a variety of risk segments of the population;
  - enhancing laboratory capacity with appropriate quality control;
  - developing affordable alternatives to viral load and CD4+ cell counts for monitoring treatment efficacy and toxicity;
  - developing clinical capabilities;
  - improving capacity for voluntary counseling and testing and partner notification;
  - funding the use of existing databases to study the natural history of HIV disease;
  - enhancing data collection and analysis capabilities;

  - funding the analysis of existing international databases and developing common data elements for new databases;
  - addressing problems in maintaining repositories of biological samples in developing countries, such as loss of electrical power to keep samples frozen;
  - developing strategies for recruitment and retention of participants into prevention, treatment, and care studies, including research on factors related to adherence, recruitment, and retention;
  - enhancing the ability to assure protection for human subjects involved in research and the ethical conduct of research, including informed consent and issues specific to mothers and children (e.g., role of the father);
  - linking HIV care to services for alcohol abuse, drug abuse, mental health, family planning, and primary care; and
  - enhancing mechanisms for information exchange among investigators, including enhanced Internet and telephone capability.

- Build global capacity to support the integration of clinical, operational, and health services research.

- Conduct studies of incidence and feasibility in order to identify sites suitable for the conduct of efficacy trials of HIV prevention, treatment, and care interventions.

Training

- Continue to support training, both in-country and in the United States, of clinicians, public health professionals, and scientists from developing nations to enhance the conduct of research on HIV, AIDS, STDs, and other HIV-related co-infections and malignancies, including research training related to (1) clinical aspects, (2) treatment and care (e.g., clinical trials of therapeutic strategies for HIV and endemic co-infections), (3) development and testing of vaccine candidates, (4) impact of alcohol and other substance abuse/dependence on HIV transmission, (5) HIV-related reproductive health, (6) disease progression, (7) prevention of MTCT, and (8) other biomedical, social, and behavioral prevention research.

- Enhance training in translational and operational research, including implementation and evaluation of prevention intervention strategies, treatment and care approaches, and feasible, cost-effective surveillance systems.
- Provide training in data management and analysis for in-country research personnel.
- Develop in-country training partnerships, and support "south-to-south" training to enable investigators to obtain training appropriate for the areas in which they will work by (1) developing in-country professionals and (2) providing opportunities to enable trained investigators returning to their home countries to serve as training resources for others.
- Enhance training to develop clinical capability and to facilitate technology transfer, including the delivery of ART; provide opportunities for foreign researchers to visit U.S. programs that serve as both models of quality care and sites for clinical studies.
- Provide training to ensure that clinicians and other health care workers understand infection control principles and can implement proper procedures in resource-poor settings.
- Ensure training that specifically includes the requirements of GCP.
- Provide training and technical assistance in the preparation of grant proposals and management of grants, including reporting requirements.
- Provide training in manuscript writing.
- Implement mechanisms to overcome language barriers so that investigators in non-English-speaking countries can have more open access to NIH grants.
- Expand training to address research administration, fiscal accountability, research support services, and grants management.
- Provide training in the ethical conduct of research, including informed consent and other topics related to the protection of human subjects.
- Encourage U.S. researchers to participate on-site in research in resource-poor settings to more fully understand the challenges of conducting research and providing care and services in such settings.

Collaboration and Coordination

- Enhance coordination of NIH international research efforts.
- Coordinate NIH AIDS and non-AIDS research efforts, particularly where projects are active in the same country and/or region.
- Encourage the continued development of collaborations between international and U.S. investigators, ensuring that research projects are relevant to strategic planning at the local level, to maximize the research effort in resource-limited settings.
- Enhance collaboration by providing competitive travel funds for attendance by foreign investigators at important scientific conferences to learn about the latest scientific findings and meet potential collaborators.
- Support mechanisms, such as "re-entry grants," to fund research activities of trained foreign investigators returning to their countries.
- Ensure the leadership role of in-country investigators and policy-level individuals in countries where studies take place by involving them in all stages of the research, including conceptualization of the research question, study design, development of protocols, study implementation and collection of data, data analysis, publication and presentation of research results, and interaction with the media.
- Provide assistance to foreign collaborators in addressing regulatory issues and special oversight mechanisms.
- Work with other U.S. Government agencies, including the Centers for Disease Control and Prevention (CDC) and the U.S. Agency for International Development (USAID), foreign governments, international organizations, NGOs, Global Fund for AIDS, TB, and Malaria (GFATM) recipients, and industry to facilitate development and testing of vaccines, microbicides, drugs, and other prevention, care, and treatment strategies, including behavioral interventions.
- Work with other U.S. Government agencies, foreign governments, international organizations, NGOs, GFATM recipients, and industry to make effective interventions resulting from research available to study participants and host-country populations.

- Explore collaboration with indigenous health providers to facilitate accomplishment of research objectives, including enhancing the participation of indigenous populations in research and improving understanding of the complexities of addressing diseases in diverse geographical settings.
- Develop programs that foster understanding of science, the role of research, and attendant ethical issues in order to enhance reporting of AIDS issues relative to geographical areas heavily impacted by the pandemic by (1) strengthening the skills of in-country and U.S. scientists in communicating effectively to the media and (2) educating the media to report on health research issues.
- Train policymakers in using research to affect policy.
- Expand NIH resources and expertise needed to manage and conduct international research.
- Involve experienced international researchers (both U.S. and host country) in development of international research programs, including soliciting advice on appropriate funding and administrative mechanisms, based on an understanding of challenges and constraints in diverse social, cultural, and resource-poor settings.
- Initiate a formal dialogue among NIH program staff, regulatory organizations, and experienced international researchers (both U.S. and host country) regarding the appropriate application(s), in international settings, of U.S. regulatory requirements, with the goals of optimizing ethics (including informed consent), science, and prevention in settings that differ from those of the United States.

Ethical Issues

- Ensure that research projects are designed to benefit the countries in which the research is being conducted.
- Enhance the capability of foreign institutions to conduct independent scientific and ethical reviews.
- Ensure education/cross-fertilization between developing country ethical review committees and U.S. institutional review boards (IRBs), and educate IRBs about cultural issues in developing countries.
- Ensure the participation of local communities, NGOs, and governments in the development of research protocols.

- Ensure that ethical challenges in both research and the implementation of research results in resource-limited settings are clearly described and addressed in grant proposals.
- Consider the need for study participants and their communities in host countries to have maximum possible access to any preventive or therapeutic products developed during the research, and initiate dialogue with pharmaceutical companies early in the clinical trials planning process in resource-limited settings.
- Ensure confidentiality of information about HIV-infected substance abusers, including information on individuals in treatment for substance abuse.
- Include a certain percentage of individuals as members of AIDS study sections who know the importance of cultural factors and/or those who have worked in developing countries.
- Consider allowing local models of human subjects review in foreign countries to be accepted as equivalent to U.S. standards.
- Ensure that ethical review mechanisms, such as consent forms, are relevant to the country where the research is conducted and are placed in cultural context.
- Conduct workshops on ethical principles and their implementation in research, encouraging countries to develop their own set of ethical guidelines and procedures, to include the principles of respect for persons, beneficence, and justice, and the application of informed consent, assessment of risks and benefits, and selection of subjects.
- Conduct training in ethical issues and how to address them in grant applications.
- Encourage in-country scientists and leaders to work closely with local journalists to foster understanding of science, the role of research, and attendant ethical issues.
- Conduct research designed to identify ways to improve the application of ethical principles in the conduct of research in varied cultural settings, including a focus on informed consent.
- Fund studies on new models for IRB review.

Technology Transfer

- Provide improved access to information through enhanced information technology.
- Transfer clinical, laboratory, and public health technologies that may be sustained and used for implementation of prevention, symptom management, clinical training, and patient care programs once research studies are completed.

Funding Mechanisms

- Develop creative and innovative approaches and mechanisms to provide funding for infrastructure development and for rapidly launching clinical trials, including improvement of space for confidential counseling, clinical care, and laboratory investigations (e.g., Clinical Research Centers).
- Design flexible and rapid mechanisms to permit conduct of expanded prevention clinical trials when preliminary studies indicate that a product or approach merits full-scale evaluation.
- Continue to explore new funding approaches for international research, including direct funding of overseas investigators and provision of indirect costs to foreign institutions.
- Continue to address indirect cost issues.

OBJECTIVE - B:

Establish the most effective, affordable, practical, and sustainable approaches to care for HIV-infected adults, adolescents, and children in resource-limited settings, including diagnosis and treatment of HIV and related conditions, such as TB, hepatitis C, and other endemic co-infections, malignancies, other STDs, neurological conditions, and nutritional deficiencies.

STRATEGIES:

Treatment of HIV with Sustainable Antiretroviral Therapy

- Determine affordable, safe, and effective ART regimens, including timing of initiation and appropriate drugs, that can be used in specific populations (e.g., adults, children, and adolescents) in diverse resource-poor geographic settings.
- Determine cost-effectiveness of ARVs in developing countries.
- Determine the pharmacokinetics of ARVs in various populations, including children.
- Investigate the impact of co-infections with other endemic diseases on the use of ART.
- Study drug-drug interactions among ARVs, medications for other endemic diseases, malignancies, and neurological and substance abuse therapies; traditional medicines; and medications or substances used for nonmedical reasons, as well as interactions with vaccines in standard use.
- Investigate interactions between HIV therapeutics, alcohol, drugs of abuse, or medications used for the treatment of substance abuse in pregnant women; evaluate the impact of such interactions on the maintenance of anti-addiction therapy and on MTCT.
- Study the impact of the use of nevirapine for preventing MTCT on response to ARVs in women who subsequently receive non-nucleoside reverse transcriptase inhibitor-containing highly active antiretroviral treatment (HAART) regimens.
- Support the long-term followup of children exposed to ART *in utero* and/or postpartum to evaluate possible late effects of exposure.
- Study treatment efficacy, side effects, and toxicity of ARVs in pediatric populations.

- Study drug compliance in children, especially as they move into and through adolescence.
- Assess the impact of nutritional status and nutritional interventions on patient survival and the efficacy and tolerability of ART.
- Study the impact of nutritional supplementation on the rate of immune system deterioration in HIV-infected persons in relation to ART.
- Determine the efficacy of ART regimens on various clades prevalent around the world.
- Examine the potential use of HIV vaccines in the context of suppressive ART.
- Study the impact of HIV vaccines on HIV disease progression in relation to initiation of ART.
- Develop and evaluate suitable, sustainable approaches for monitoring treatment efficacy, side effects, and toxicity, with particular emphasis on finding affordable CD4+ cell counts and HIV load methodologies, as well as suitable alternatives.
- Determine the impact of ART on development of drug-resistant strains of HIV in diverse geographical settings, and develop strategies to limit its development.
- Develop and test appropriate measures and study levels of and barriers to adherence to HIV medications.
- Develop and test strategies to support adherence to medication to enhance therapeutic outcomes and to limit the development of drug resistance.
- Examine the effectiveness of a variety of approaches to the administration of therapy (e.g., directly observed therapy or directly delivered therapy).
- Assess the impact of ART on HIV transmission and prevalence, including associated behavior change, in various communities.
- Determine the social, psychological, societal, and economic impact of ART on individuals (including children), families, and communities, including the impact on personal risk behavior.

- Identify conditions that emerge as a consequence of ART and longer survival, such as malignancies, neurological and neuropsychological conditions, and metabolic and nutritional dysfunction.
- Determine whether expanded ARV care and treatment lead to a decrease in HIV-associated stigma.
- Develop strategies to ensure that prevention efforts in resource-limited countries are simultaneously preserved and enhanced when clinical trial, and later ART treatment, programs are established.
- Study the impact on implementation of ART of prior use of traditional medicine.

Sustainable Strategies for Preventing and Treating Endemic Co-infections and Other HIV-Related Conditions

- Define the spectrum, incidence, and risk factors for HIV-related illnesses (e.g., endemic co-infections such as TB and hepatitis C, malignancies, and neurological conditions) in adult, adolescent, and pediatric populations specific to individual regions in diverse geographic settings.
- Study the variability in the natural history of HCV infection among different genotypes and the different rates of co-infection with HIV.
- Develop simple, cost-effective, and sustainable diagnostic tests for endemic co-infections and other conditions, such as TB and hepatitis C.
- Investigate sustainable strategies for preventing, treating, and monitoring response to treatment of endemic co-infections and other HIV-related conditions.
- Assess the impact of available antibiotic treatment and prophylaxis regimens to optimize therapeutic approaches for TB and other endemic co-infections, including new therapies for TB and new approaches to administering drugs.
- Determine the safest and most efficient treatment modalities for endemic co-infections (e.g., TB, hepatitis C, leishmaniasis, dengue fever, and malaria) in the pediatric/adolescent populations.
- Study drug-drug interactions among drugs used to prevent and treat endemic infections.

- Develop simple clinical algorithms for guiding initiation of prevention or treatment of infections.
- Identify affordable means to target high-risk patients for initiation of prophylaxis.
- Develop methods to monitor development of antimicrobial resistance by HIV-related and endemic pathogens infecting both study participants and the general population.
- Identify strategies to limit development of drug resistance, including studies of adherence.
- Develop strategies to enhance and monitor adherence to therapy/prophylaxis for endemic co-infections.
- Determine the safety and effectiveness of available immunizations in diverse HIV-infected populations.
- Assess the burden of TB and the relative importance of reactivation versus *de novo* infection in various settings.
- Conduct studies to better understand the role and mechanism of re-infection and/or superinfection with HCV.
- Study neuropsychiatric problems in specific HIV-infected populations (e.g., women, children, and adolescents).
- Study STDs and other gynecological problems in HIV-infected women and girls.
- Study ophthalmological problems in HIV-infected children.

Approaches to Care

- Determine barriers and facilitators to acceptance of HIV testing and treatment and/or prevention recommendations.
- Develop culturally appropriate mechanisms to identify persons for whom treatment is indicated, and to overcome factors such as stigma, which can forestall testing and limit the provision of treatment and care.
- Continue to identify better, low-cost alternatives for diagnosis of HIV.

- Develop better approaches to voluntary counseling and testing that encourage knowledge of one's status and help mitigate social harm, including changing community norms about acceptance of persons living with AIDS.
- Identify clinical management approaches, including effective palliative care strategies, and overall care needs among HIV-infected persons in diverse settings.
- Develop and evaluate care models, such as family models of care, and enhance interdependent care services that integrate AIDS care into existing programs, such as TB control programs, alcohol and other substance abuse/dependence treatment programs, and maternal and child health services, to avoid duplication of efforts.
- Develop and evaluate strategies to initiate and provide care to targeted groups of individuals, such as health care workers, security forces, and teachers.
- Develop TB prevention and education strategies for use with HIV-infected individuals, as well as the general population.
- Develop interventions to mitigate the negative social consequences of HIV infection, including AIDS stigma, with particular emphasis on children affected by or infected with HIV (AIDS orphans).

Crosscutting Strategies

- Continue to characterize the natural history of HIV infection in diverse geographic settings.
- Examine the role of co-infections with other endemic diseases in modulating HIV, including risk of acquiring and/or transmitting infection and disease progression.
- Assess the impact of treatment for HIV infection on the natural history of HCV infection and the impact of treatment for HCV infection on the natural history of HIV infection.
- Support operations research to facilitate the translation of research findings to clinical practice and public health programs and to provide information to inform the scale-up of programs.

OBJECTIVE - C:

Develop, adapt, and evaluate comprehensive biomedical, behavioral, social, and structural prevention interventions appropriate for use in diverse cultural, geographical, and political settings.

STRATEGIES:

Blood-Borne Transmission

- Evaluate the risk of transmission of HIV and other blood-borne pathogens through contaminated blood and medical accidents, including iatrogenic transmission.
- Develop strategies to prevent blood-borne transmission of HIV and HCV in health care settings, including recruitment and retention of appropriate blood donors, predonation counseling of all blood donors, improvement of blood screening strategies and technologies, and appropriate use of transfusion.
- Encourage research on the relationship between the use of paid and/or professional blood donors and the dynamics of the spread of HIV infection.
- Encourage research on the role of plasma and the spread of HIV infection.
- Develop strategies to improve implementation of universal precautions.
- Develop strategies to prevent blood-borne transmission of HIV and HCV through inappropriate or unsafe use of injections in and outside the health care setting.

Sexual Transmission

- Establish the most effective and sustainable ways to change or prevent high-risk sexual behaviors, such as multiple partners, rape, trafficking of women and children into forced sex work and commercial sex work, and substance use and abuse that foster the spread of HIV and STDs in resource-limited settings.
- Develop interventions targeted to both HIV-positive and HIV-negative persons and that are designed to appeal to specific populations, such as women, men, adolescents, and the military.

- Develop biomedical strategies to prevent HIV transmission by high-risk sexual behaviors, including the continued development of microbicides; studies of other preventive strategies, such as barrier methods and the factors affecting their use; syndromic management of STDs; and the cost-effectiveness of such strategies.
- Investigate the effectiveness of community-based and community-level HIV prevention programs, including prevention education based on abstinence and monogamous relationships and strategies to evaluate, replicate, and extend effective behavioral interventions.
- Develop and test prevention interventions to be used in the family context to prevent risky behavior and HIV acquisition and transmission by its members.
- Perform research into the culturally appropriate content, form, and format of instruments that will improve the quality of culturally appropriate self-reports of sexual risk behaviors.
- Improve clinical management of viral sexually transmitted infections, emphasizing co-infections with herpes simplex virus (HSV)-2 and human papillomavirus (HPV).
- Study gender-related biological factors affecting susceptibility to infection, including the use of hormonal contraceptives and the presence of gender-specific conditions, such as HPV infection and cervical cancer.
- Examine the role of co-infection with other endemic diseases in modulating HIV, including risk of acquiring and/or transmitting infection and disease progression.
- Study the impact of ART on preventive behaviors.
- Study the role of sexual transmission of HCV in co-infection with HIV.

Substance Use

- Investigate the role of alcohol and other commonly used psychoactive substances in promoting or facilitating sexual risk behaviors and as intervening factors that act as barriers to prevention, to reduce the efficacy of prevention strategies, and to enhance other risks for HIV, such as STDs.

- Investigate the impact of alcohol abuse, drug abuse, and other associated co-morbid conditions on HIV disease progression, adherence to treatment regimens, and clinical outcomes.
- Devise strategies to prevent initiation of drug use, alcohol dependence, and transition to riskier drug practices, such as initiating drug injection and sharing of injection equipment.
- Conduct studies to identify sustainable interventions at the levels of the individual, social network, community, and society to prevent HIV and HCV transmission as a result of high-risk sexual activity and/or drug use practices associated with alcohol and drug use.
- Evaluate innovative, culturally relevant, contextually appropriate alcohol and drug abuse treatment programs for their utility as HIV and HCV prevention approaches in different international settings.
- Determine the factors involved in the injecting and noninjecting drug user's and heavy drinker's social networks that influence the rate and patterns of diffusion of HIV infection, and design prevention programs based on the results.
- Conduct comparative epidemiological studies of substance use and risk for HIV and HCV in settings of varying cultural conditions and HIV seroprevalence.
- Evaluate the effectiveness of expanded access to needle and syringe exchange programs.
- Develop approaches for drug and alcohol abuse programs among HIV- and HCV- infected patients to improve adherence with drug/alcohol treatment strategies.

Mother-to-Child Transmission: Considerations for the Mother, Infant, and Child

- Develop safe, effective, feasible, and conveniently administered strategies to interrupt MTCT, using interventions that are affordable and can be implemented in resource-poor nations, including specific strategies to prevent postnatal transmission of HIV through breast milk by providing prophylaxis to the infant, mother, or both during the lactation period.

- Develop and evaluate strategies for reducing the risk of MTCT without compromising treatment of the pregnant woman, including adherence to ART in the context of MTCT programs, the consequences of intrapartum ART on continued treatment regimens of ARVs, and the impact on subsequent pregnancies.
- Study the effect of ARV regimens used for maternal health indications on the risk of MTCT (including postnatal transmission through breast milk) and other outcomes, including pregnancy outcomes.
- Investigate the mechanisms and timing of MTCT (*in utero*, intrapartum, and postpartum via breast milk) to facilitate and develop targeted drugs/strategies to further decrease MTCT or provide alternatives to currently identified effective strategies.
- Further identify cost-effective, nondrug regimens for preventing MTCT, such as research on infant feeding, including:
  - acceptability of safe breastfeeding alternatives;
  - impact of the use of breast milk alternatives on morbidity and mortality of both the mother and infant;
  - breastfeeding and interaction with continued ART; and
  - role of exclusive breastfeeding.
- Conduct studies to evaluate and reduce short- and long-term toxicity of ARV drugs in women during pregnancy and in their offspring who were perinatally exposed.
- Investigate the unique immune status and develop immune interventions in both pregnant women and infants to interrupt HIV transmission.
- Examine the role of maternal and infant nutrition during the peripartum and postpartum periods in reducing morbidity and mortality in HIV-infected mothers and their infants and in reducing MTCT.
- Study the impact of the health status of HIV-infected mothers on the survivability of both HIV-infected and HIV-noninfected children.
- Study the impact of breastfeeding on the health status of HIV-infected mothers.

- Devise strategies to develop or use existing infrastructures to identify women at risk of HIV infection, and to implement treatment of them.

Vaccine Development

- Continue the accelerated efforts toward development of vaccine candidates suitable for use around the world, and foster the development of vaccines to optimize characteristics appropriate for broad international use, including designs exhibiting low cost with ease of production and administration, as well as stability.

- Define immune approaches that will provide specific and sustained protection against HIV transmission; develop the products necessary to achieve these goals; and develop the capacity to evaluate their safety in human subjects.

- Provide a solid scientific knowledge base (incidence, viral subtypes, major histocompatibility [MHC] types, natural history) to justify clinical trials in international sites and to conduct trials in these sites and communities according to the highest clinical and ethical standards.

- Identify suitable populations of adults and children in which to evaluate candidate vaccines.

- Conduct Phase I, Phase II, and Phase III trials for safety, immunogenicity, and efficacy with suitable candidate vaccines or concepts in domestic and international settings.

- Enlist participation of local representatives in the development of appropriate trial protocols as well as responsive mechanisms to inform and educate the participating individuals; establish networks within the community that will effectively, and on a continuing basis, address the social and medical concerns of the participants; and establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale of the study.

- Examine relevant behavioral issues related to the conduct of vaccines research and acceptability in diverse populations.

- Conduct research on the social and economic impact of vaccines and their cost-effectiveness.

Crosscutting Strategies

- Develop sustainable behavioral, economic, and environmental interventions to address the multiple risk factors present in selected populations.
- Study the impact on HIV transmission of social and structural issues such as famine and migration due to labor or forced displacement of people through war.
- Conduct multidisciplinary prevention research in multiple settings, including medical treatment and community support and care organizations, enhanced by rapid assessments of at-risk groups identified in each local geographic context.
- Conduct research to integrate the multiple components of diverse issues of sexuality, alcohol and other substance use, and mental health into HIV prevention programs.
- Encourage research on mechanisms to integrate prevention and care services and on the impact of integration and the organization of health services at the public health level, including evaluation, dissemination, and expansion of model programs.
- Develop new approaches to voluntary counseling and testing and assess them for cost-effectiveness and impact on reducing risk from sexual behavior and drug use in settings with varying levels of seroprevalence.
- Study gender-related social and behavioral factors affecting acquisition of infection, such as economic power imbalances between the sexes.
- Evaluate strategies to reduce stigma and increase willingness of individuals to (1) enter into voluntary counseling and testing, (2) identify, accept, and undertake alternative infant feeding practices, and (3) enter ART.
- Develop biomarkers that can serve as surrogates for measurement of HIV risk behavior and can be used to predict and monitor rapid escalation of HIV epidemics.
- Identify biological determinants of infectiousness and susceptibility to infection, including both viral and host factors.

- Study gender-related biological factors affecting susceptibility to infection, including the use of hormonal contraceptives and the presence of gender-specific conditions such as HPV infection and cervical cancer.
- Utilize population-based studies to examine basic scientific questions about HIV, mechanisms of transmission, and host response, including viral evolution, viral diversity, human immunology, and mucosal factors in transmission.
- Conduct research on how best to deliver prevention education in the care setting.
- Support operations research to facilitate the translation of research findings to clinical practice and public health programs and to provide information to inform the scale-up of programs.
- Develop links with other agencies and organizations to integrate research with service programs and to develop multidisciplinary collaboration.
- Study the psychological impact of HIV infection in women, including their role as heads of households and/or caregivers, the impact of additional pregnancies, and family support.

OBJECTIVE - D:

Enhance the translation of research results for the improvement of patient management, development of prevention programs appropriate and acceptable to specific settings, and to inform in-country policy decisions around the world by conducting translational and operational research on implementation, including: (1) local logistical problems, (2) social and behavioral risks of HIV transmission specific to each regional population, (3) regional economic and political realities, (4) long-term sustainability of research infrastructure and cohorts, (5) full community participation in research planning and implementation, and (6) ethical issues within cultural realities.

STRATEGIES:

- Conduct translational and operational research to accomplish widespread delivery of interventions to prevent transmission and acquisition of HIV infection and to provide care and treatment for those individuals and families affected by HIV (e.g., (1) ART; (2) HIV vaccines; (3) microbicides; (4) treatment and prophylaxis of endemic co-infections, including TB and hepatitis C; (5) other products; (6) behavioral and other interventions, such as syndromic management of STDs and breastfeeding practices, including logistical issues on how to scale up from research projects; and (7) drug and alcohol abuse treatment).
- Continue to characterize behavioral, social, and structural risk factors (including cross-border issues) for transmission of HIV in specific populations and geographic areas.
- Investigate the relative benefits of various approaches to provision of care and treatment.
- Develop strategies for integrating the delivery of HIV care with drug treatment, alcohol treatment, TB treatment, and other medical and social services commonly needed by HIV-infected people.
- Conduct studies, including clinical trials, on quality of care.
- Conduct research on how to scale up from pilot projects and/or early Phase I and II trials to large research populations, including Phase III trials.
- Conduct studies on effectiveness as well as efficacy.

- Conduct research on how to scale up from research studies to implementation of programs, including addressing the tension between fidelity and flexibility in scaling up.
- Develop criteria for different aspects of sustainability of potential interventions that can be used to determine priorities for research.
- Educate investigators to address sustainability of technologies in grant proposals.
- Integrate operational and health services research with clinical research to facilitate the translation of research findings into clinical practice and public health programs, addressing HIV in the context of other diseases, access to health care, and prevention programs.
- Identify models for sustainability and integrate research with sustainable treatment and care by coordinating U.S. research efforts with efforts of other governments, CDC, WHO, USAID, NGOs, and recipients of funding from the GFATM.
- Develop models for communication among agencies.
- Ensure the integration of U.S. research programs with established country programs, including collaboration with local investigators on strategic planning.
- Involve developing country partners, including policymakers, Ministries of Health, academic medical institutions, local investigators, and community advisory board (CAB) members in the development and prioritization of research agendas pertinent to their setting.
- Develop a forum for developing country partners, including policymakers, Ministries of Health, academic medical institutions, local investigators, and CAB members, to discuss and identify potential areas of research needed in the development and design of clinical trials and the subsequent implementation of research results in programs and policies.
- Strengthen CABs to participate in the development and design of clinical trials and other research, as well as in the translation of research results into programs and policies.
- Devise approaches to educate policymakers about research findings that are appropriate to their settings.

- Develop distance learning approaches to enhance communication of research results and translation into prevention, treatment, and care programs.
- Provide improved access to information concerning treatment and prevention guidelines and the results of research through enhanced information technology.
- Develop and provide access to guidelines for implementation of research results.
- Develop regional approaches to research (e.g., through regional meetings) to enhance communication and to address common problems and needs among countries in the region.
- Facilitate development of HIV prevention and treatment guidelines, adding behavioral, basic, and epidemiological aspects to clinical findings.
- Conduct research on the impact of political changes on the epidemic, developing special initiatives to recruit new investigators and to stimulate research in this area.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	John E. Fogarty International Center
CSR	Center for Scientific Review
NCMHD	National Center on Minority Health and Health Disparities

APPENDIX B:

FY 2005 OAR Planning Group for International Research

FY 2005 INTERNATIONAL RESEARCH PLANNING GROUP

Non-NIH Participants

Nancy Padian, Ph.D., M.P.H., M.S., Co-Chair
Professor
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Celia D.C. Christie, M.D., M.P.H.
Professor of Pediatric Infectious Diseases
University of the West Indies

Myron S. Cohen, M.D.
Chief
Department of Infectious Diseases
University of North Carolina at Chapel Hill

Yvette Delph, M.D.
International Program Coordinator
Adult AIDS Clinical Trials Group
Social & Scientific Systems, Inc.

Don C. Des Jarlais, Ph.D.
Director of Research
Chemical Dependency Institute
Beth Israel Medical Center

Gerald H. Friedland, M.D.
Director
AIDS Program
Professor of Medicine and Epidemiology
Yale University

Amanda J. Gibbons, Ph.D., M.P.H.
Technical Advisor
Mother-to-Child Transmission
Office of HIV/AIDS
Bureau for Global Health
U.S. Agency for International Development

Andrzej Horban, M.D., Ph.D.
Director
AIDS Diagnosis and Therapy Center
Hospital of Infectious Diseases

Phyllis Kanki, D.V.M., S.D.
Professor
Immunology and Infectious Disease
Harvard School of Public Health

Serena P. Koenig, M.D.
Medical Director
Haiti Programs
Partners in Health
Brigham and Women's Hospital

Judith Levy, Ph.D.
Associate Professor
Health Policy and Administration
School of Public Health
University of Illinois at Chicago

Mary A. Marovich, M.D., DTMH
Physician/Investigator
U.S. Military HIV Research Program

Enawgaw Mehari, M.D.
Chief
Neurology Service
Department of Neurology
Morehead Clinic and St. Claire Hospital

Phillip Nieburg, M.D., M.P.H.
Global AIDS Program
Centers for Disease Control and Prevention
U.S. Department of Health and Human Services

William Parish, Ph.D.
Professor of Sociology
University of Chicago

Merle A. Sande, M.D.
Director
Residency Program
Department of Internal Medicine
University of Utah

Bruce D. Walker, M.D.
Director
Partners AIDS Research Center
Massachusetts General Hospital

Maria Wawer, M.D., M.H.Sc.
Professor of Clinical Public Health
Columbia University

NIH Participants

Ms. Linda Reck, Co-Chair
Senior Policy Analyst
Office of AIDS Research
Office of the Director, NIH
U.S. Department of Health and Human Services

Jodi B. Black, Ph.D.
Program Director
Division of Cancer Treatment and Diagnosis
National Cancer Institute, NIH
U.S. Department of Health and Human Services

Kendall Bryant, Ph.D.
Coordinator
AIDS Behavioral Research
National Institute on Alcohol Abuse and Alcoholism, NIH
U.S. Department of Health and Human Services

Henry "Skip" Francis, M.D.
Director
Center on AIDS and Other Medical Consequences of Drug Abuse
National Institute on Drug Abuse, NIH
U.S. Department of Health and Human Services

Rodney Hoff, D.Sc., M.P.H.
Acting Associate Director for International Research
Division of AIDS
National Institute of Allergy and Infectious Diseases, NIH
U.S. Department of Health and Human Services

Barbara E. Laughon, Ph.D.
Chief
Complications and Co-Infections Research Branch
Therapeutics Research Program
Division of AIDS
National Institute of Allergy and Infectious Diseases, NIH
U.S. Department of Health and Human Services

Eugene O. Major, Ph.D.
Acting Deputy Director
National Institute of Neurological Disorders and Stroke
Chief
Laboratory of Molecular Medicine and Neuroscience
National Institute of Neurological Disorders and Stroke, NIH
U.S. Department of Health and Human Services

Jeanne McDermott, Ph.D., C.N.M., M.P.H.
Program Officer
Division of International Training
and Research
John E. Fogarty International Center, NIH
U.S. Department of Health and
Human Services

Lynne M. Mofenson, M.D., FAAP
Chief
Pediatric, Adolescent and Maternal
AIDS Branch
Center for Research for Mothers and Children
National Institute of Child Health and
Human Development, NIH
U.S. Department of Health and
Human Services

Susan Newcomer, Ph.D.
Statistician
Demographic and Behavioral Science Branch
Center for Population Research
National Institute of Child Health and
Human Development, NIH
U.S. Department of Health and
Human Services

Willo Pequegnat, Ph.D.
Associate Director of Prevention, Translational
and International Research
Division of Mental Disorders
Behavioral Research and AIDS
National Institute of Mental Health, NIH
U.S. Department of Health and
Human Services

Leslie K. Serchuck, M.D.
Medical Officer
Pediatric, Adolescent and Maternal
AIDS Branch
National Institute of Child Health and
Human Development, NIH
U.S. Department of Health and
Human Services

APPENDIX C:

List of Acronyms

LIST OF ACRONYMS

ACSR	AIDS and Cancer Specimen Resource, NCI
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ART	antiretroviral therapy
ARV	antiretroviral
ATI	analytic treatment interruption
ATIS	AIDS Treatment Information Service
AVEG	AIDS Vaccine Evaluation Group
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CAPS	Center for AIDS Prevention Studies (University of California, San Francisco)
CBO	community-based organization
CDC	Centers for Disease Control and Prevention
CIPRA	Comprehensive International Programs for Research on AIDS
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocyte
DC	dendritic cell
DHHS	Department of Health and Human Services
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
GBV-C	GB virus (hepatitis G)
GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GFATM	Global Fund for AIDS, Tuberculosis, and Malaria

GI	gastrointestinal
GLP/GMP	good laboratory practice/good manufacturing practice
GRIP	Global Health Research Initiative Program, FIC
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Universities
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV	human herpesvirus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV	herpes simplex virus
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IND	investigational new drug
IRB	institutional review board
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus
LRP	Loan Repayment Program, NIH
MAb	monoclonal antibody
MAC	*Mycobacterium avium* complex
MDR-TB	multidrug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
MTCT	mother-to-child transmission
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organization

NHL	non-Hodgkin's lymphoma
NHP	nonhuman primate
NIH	National Institutes of Health
NK	natural killer (cell)
NMAC	National Minority AIDS Council
NNTC	National NeuroAIDS Tissue Consortium, NIMH/NIDA/NINDS
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
PACTG	Pediatric AIDS Clinical Trials Group
PCP	*Pneumocystis carinii* pneumonia
PML	progressive multifocal leukoencephalopathy
RCT	randomized clinical trial, randomized controlled trial
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	structured treatment interruption; sexually transmitted infection
TB	tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	U.S. Agency for International Development
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WRAIR	Walter Reed Army Institute of Research

Office of AIDS Research, National Institutes of Health
Building 2, Room 4W01 (MSC 0255)
Two Center Drive, Bethesda, Maryland 20892
Tel: 301-402-8655, Fax: 301-402-8638

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